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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,779	11/30/2001	Kenneth Chien	6627-PA9025	3690

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	16

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/830,779	Applicant(s) Chien et al
	Examiner Patricia A. Duffy	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 17, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *4, 12, 14, 16, and 18-23* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *4, 12, 14, 16, and 18-23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The response filed 3-17-03 has been entered into the record. Claims 4, 12, 14, 16, and 18-23 are pending.

Priority

2. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claim of this application for the treatment of heart failure or enhancement of cardiac contractility by addition of an exogenous phospholamban protein/mutant or truncated version thereof.

Information Disclosure Statement

3. The information disclosure statement filed 8-13-01 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56© most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered with respect to the foreign language document.

Election/Restriction

4. Applicant's election with traverse of Group I, species mutant PLB in Paper No. 9 is acknowledged. The traversal is on the ground(s) that proteins PLB, mutant PLB and truncated PLB are linked by structure and function and are therefore not separate species

as set forth by the examiner. This is found persuasive. All pending claims will be examined. *It is noted that claims will be examined to the extent that they read on the use of the polypeptide per se as the elected species and set forth in the lack of unity requirement.*

Claim Rejections - 35 U.S.C. § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 4, 12, 14, 16, and 18-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of inducing PLB deficiency wherein an exogenous PLB protein induces phospholamban deficiency or method of treatment of heart failure comprising enhancement of cardiac contractility wherein exogenous PLB protein is used to inhibit interaction between PLB and sarcoplasmic reticulum calcium ATPase (SERCA2a). Applicants teach at page 2, second full paragraph that activity of the cardiac sarcoplasmic

reticulum Calcium ATPase (SERCA2a) is regulated by phospholamban (PLB), a 52 amino acid muscle-specific sarcoplasmic reticulum phosphoprotein. The specification also teaches that PLB exists primarily in a pentameric form and that when subjected to high temperature, dissociates into five equivalent monomers (page 3, lines 3-6). It is noted that the sarcoplasmic reticulum is a organelle that lies completely inside muscle cells and surrounds myofibrils. The sarcoplasmic reticulum is surrounded by the cell cytosol and the sarcoplasmic reticulum is surrounded by and separate from the plasma membrane (see pages 825-827 of Darnell et al, Molecular Cell Biology, Scientific American Books, Inc. 1986). Applicants acknowledge at page 5, lines 7-10, that the internalization of exogenous molecules to enhance cardiac contractility by live myocytes remains an unresolved issue. The specification is devoid of any teachings that indicate that this problem has been actively solved, either *in vitro* or *in vivo*. The specification further teaches that the non-phosphorylated PLB inhibits SERCA2a (page 11, lines 16-20). While the specification teaches gene-mediated ablation of endogenous PLB in a double-knockout mouse enhances cardiac contractility, there is no teaching of how to apply, administer a exogenous PLB protein, PLB mutant or truncated PLB in order to induce PLB deficiency as claimed. As recited in the specification, PLB is a 52 amino acid protein having a molecular weight approximately of 5200 Daltons. Proteins/peptides of this size are specifically excluded from cells by means of the plasma membrane. The specification does not teach that these polypeptides when applied exogenously either *in vitro* or *in vivo*: (a) do in fact enter the cardiac myocyte and (b) enter in sufficient quantities to treat heart disease or enhance cardiac contractility. Even if one were to demonstrate post filing that the claimed exogenous PLB proteins entered cardiac myocytes in vitro, the in vivo situation is highly complex. As set forth in the specification, PLB is not specific to cardiac myocytes (cardiac

muscle cells), but to myocytes (i.e. muscle cells) in general and as such, if taken up by cardiac muscle cells would also more likely than not, be taken up by other muscle cells. It is noted that cardiac muscle mass is a small component of the total muscle mass of an average adult (skeletal muscle + smooth muscle + cardiac muscle). In a non-specific means of uptake all of these muscles would take up the exogenous PLB protein/mutant/truncated form and as such it is not clear from the specification as filed whether there can be sufficient administered in any manner, to achieve the goals of the claims (i.e. induction of phospholamban deficiency or enhancement of cardiac contractility). Unlike gene-mediated transection of cells (i.e. the non-elected invention), there is no constant production of the protein in the cells and therefore it is not readily apparent that sufficient protein can be administered *in vivo* or *in vitro* to provide the functionality as claimed. The courts have held ".. in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provide broad enablement in the sense that once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictably of factors involved." *(In re Fisher* 166 USPQ 18 (CCPA)). The state of the art at the time of filing was unpredictable and remained unpredictable post filing. Applicants have not demonstrated that the claimed method will operate either *in vitro* or *in vivo* and Applicants acknowledge at page 5, lines 7-10, that the internalization of exogenous molecules to enhance cardiac contractility by live myocytes remains an unresolved issue. Although Applicants have provided a general strategy, due to the unpredictable nature of the art and the uncertainty in the field of exogenous protein used to treat cardiac disease, it does not appear that the general teachings are sufficient to

enable the ordinary skilled artisan to either make or use the claimed inventions. Applicant has not provided the expected range of results, statistics, the predictability of the claimed composition/methods for the skilled artisan. While working examples are not required, the presence or absence of working examples has been held to be a factor for the determination of undue experimentation by the Forman Board (See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986) as cited in *In re Wands* (CAFC) 8 USPQ2d 1400). In reaching a conclusion of undue experimentation, the following factors have been considered: quantity of experimentation necessary, amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the stat of the prior art, relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims (*In re Wands* (CAFC) 8 USPQ2d 1400). Further, the courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* (CCPA) 153 USPQ 48). Inasmuch as, normal cells exclude polypeptide of the lengths of PLB/mutants/truncants and that the specification fails to demonstrate that exogenously added PLB can enter the cells and enter the cells in an amount sufficient to function as claimed, it would require undue experimentation on the part of the skilled artisan to make and use the invention as claimed. While the skill in the art is high

8. Claims 4, 12, 14, 16, and 18-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite "...comprising inducing phospholamban deficiency, wherein in an exogenous phospholamban (PLB) protein induces phospholamban deficiency...". These claims are prima facie indefinite because it does not indicate how the exogenous PLB protein

induces phospholamban deficiency. Is it administered intravenously, coated on the skin patient, given by cardiac catherization ? How is the exogenous protein used to induce phospholamban deficiency or enhance cardiac contractility ? As such, the skilled artisan would be unable to ascertain how to use PLB protein to achieve the goal of the preamble. Correction is required.

Citation of Relevant Art

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. These references demonstrate the complexity of treating heart disease and the differential effects of different exogenously added mediators on PLB and heart contractility

A. Takeishi et al (Am. J. Phsiol. 276:H53-H62, 1999).

B. Sommerschild et al (J. Mol. Cell. Cardiol. 31:1897-1911, 1999).

C. McTiernan et al (Circ. Res., 81:493-503, 1997).

D. Yokoyama et al (J. Mol. Cell. Cardiol. 31:261-273, 1999).

E. Kimura et al. (J. Mol. Cell. Cardiol. 26:1145-1154, 1994).

Status of Claims

10. No claims are allowed.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should

applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
June 1, 2003

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600